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Jaundice: A basic-review

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Abstract
Jaundice is not a disease rather a clinical condition that may occur in many different diseases due to excessive deposition of bilirubin in the body resulting in yellowish colouration of skin, sclera and mucous membranes. Jaundice is considered as an essential clinical indicator for liver disease, apart from various other insults. However, it is important to determine the underlying cause of jaundice whether it is congenital or acquired. A detailed medical history and physical examination initiate the diagnosis process followed by detailed clinical, laboratory, and imaging examinations in order to determine the etiology of jaundice and accordingly adequate treatment resume followed. So, the article aims to provide basic ideas on the pathophysiology, diagnosis and treatment of jaundice.

Keywords: Jaundice, bilirubin, pathophysiology, diagnosis, treatment

Introduction
Jaundice is derived from French word *'Jaune'* meaning yellow. Jaundice is also known as icterus. Jaundice is a clinical condition characterized by yellow color of the white of the eyes (sclerae) and skin. lt is caused by the deposition of bilirubin due to its elevated levels in the serum (Satyanarayana and Chakrapani 2022) [1]. The term hyperbilirubinemia is often used to represent the increased concentration of serum bilirubin (Schwarzenbach 2013) [2]. Deposition of bilirubin happens only when there is an excess of bilirubin, a sign of increased production or impaired excretion. The normal serum levels of bilirubin are less than 1mg/dl; however, the clinical presentation of jaundice as scleral icterus (peripheral yellowing of the eye sclera), is best appreciated only when the levels reach more than 3 mg/dl. Sclerae have a high affinity for bilirubin due to their high elastin content (Leung *et al.* 2019) [3]. With further increase in serum bilirubin levels, the skin will progressively discolor ranging from lemon yellow to apple green, especially if the process is long-standing; the green color is due to biliverdin (Roche and Kobos 2004) [4]. Bilirubin has two components: unconjugated (indirect) and conjugated (direct), and hence elevation of any of these can result in jaundice. Icterus acts as an essential clinical indicator for liver disease, apart from various other insults (Vítek and Ostrow 2009) [5]. Yellowing of skin sparing the sclerae is indicative of carotenoderma which occurs in healthy individuals who consume excessive carotene-rich foods (Al Nasser *et al*. 2022) [6].
The clinical sign of icterus or jaundice develops when the yellow pigment bilirubin accumulates in plasma and other tissues. Yellow discoloration of tissues can first be noted by careful observation when the plasma bilirubin value exceeds 2 to 3 mg/dl and can be appreciated even by an untrained observer when the concentration exceeds 3 to 4 mg/dl. Elevated plasma bilirubin values are usually present for one or more days before clinical icterus is apparent, and there may be a delay between the time plasma bilirubin returns to normal and the clearance of the yellow discoloration of tissues. (Kaneko *et al.* 2008) [7].
Jaundice may be more appropriately considered as a symptom rather than a disease (Chennai Liver Foundation 2022) [8]. lt is rather difficult to classify jaundice, since it is frequently caused due to multiple factors. Jaundice is typically caused by an underlying pathological process that occurs at some point along the normal physiological pathway of heme metabolism. A deeper understanding of the anatomical flow of normal heme metabolism is essential to appreciate the importance of prehepatic, hepatic, and post hepatic categories. (Vítek and Ostrow 2009; Hsia 1965) [5, 9].

Pathophysiology
Prehepatic (Fate of Erythrocytes)
Erythrocytes have a life span and are removed from the circulation after completion of their

lifespan. Erythrocytes are degraded by the macrophages of the reticuloendothelial (RE) system in the spleen and liver. The hemoglobin is cleaved to the non-protein heme and protein part globin which may be reutilized as such for the formation of hemoglobin or degraded to the individual amino acids, which later participates in fresh globin synthesis.

A complex microsomal enzyme namely heme oxygenase cleaves heme to form biliverdin to biliverdin (a green pigment) which is excreted in birds and amphibian while in mammals it is further degraded to bilirubin (yellow pigment) by biliverdin reductase. The term bile pigments are used to collectively represent bilirubin and its derivatives.

Bilirubin is lipophilic and therefore is transported in the plasma in a bound (non-covalently) form to albumin. As the albumin-bilirubin complex enters the liver, bilirubin dissociates and is taken up by sinusoidal surface of the hepatocytes by a carrier mediated active transport (Satyanarayana and Chakrapani 2022; Joseph and Samant 2022) [1, 10].

Hepatic (Conjugation of bilirubin)

In the liver, bilirubin is conjugated with two molecules of glucuronate results in the formation of a water-soluble bilirubin diglucuronide by bilirubin glucuronyl transferase (of smooth endoplasmic reticulum). The conjugated bilirubin is then excreted into the bile canaliculi against a concentration gradient which then enters the bile and reaches intestine (Satyanarayana and Chakrapani 2022; Joseph and Samant 2022) [1, 10].

Post hepatic (Fate of bilirubin)

In the intestine, the conjugated bilirubin (Bilirubin glucuronides) are hydrolyzed to liberate bilirubin by specific bacterial enzymes namely β-glucuronidases. The bilirubin is then converted to urobilinogen which is a colourless compound, a small part of urobilinogen may be reabsorbed into the circulation. In kidney a part of urobilinogen is converted to urobilin which imparts characteristic yellow colour to urine and excreted out. The remaining part of urobilinogen is converted by bacteria to stercobilin which gives characteristic brown colour to the feces (Satyanarayana and Chakrapani 2022; Joseph and Samant 2022) [1, 10].

Types of Jaundice

For the sake of convenience to understand, jaundice is classified into three major types-hemolytic (prehepatic), toxic (hepatic) and obstructive (posthepatic) (Satyanarayana and Chakrapani 2022) [1].

1. Hemolytic jaundice

Hemolytic jaundice occurs due to increased hemolysis of erythrocytes (*e.g* incompatible blood transfusion, malaria. sickle-cell anemia). Therefore, hemolytic jaundice is characterized by elevation in the serum unconjugated bilirubin along with increased excretion of urobilinogen in urine and dark brown colour of feces due to high content of stercobilinogen (Satyanarayana and Chakrapani 2022) [1].

2. Toxic jaundice

Toxic jaundice is caused by any dysfunction of the liver due to damage to the parenchymal cells *e.g.* viral infection (viral hepatisis), alcohol, poisons and toxins (chloroform, carbon tetrachloride, phosphorus etc.) cirrhosis of liver, cardiac failure etc. [11] In this type of jaundice, both the bilirubin uptake as well as its conjugation is affected. Thus, hepatic jaundice is characterized by increased levels of both conjugated and unconjugated bilirubin in the serum, dark coloured urine, increased activities of alanine transaminase (SGPT) and aspartate transaminase (SCOT). Pale, clay coloured stools may be observed due to the absence of stercobilinogen (Satyanarayana and Chakrapani 2022) [1].

3. Obstructive jaundice

Obstructive jaundice occurs due to an obstruction in the bile duct which prevents the passage of bile into the intestine. The obstruction may be caused by gall stones, pancreatic tumors, biliary atresia, a congenital condition associated with abnormal development or the bile ducts etc. (Hsia 1965) [9]. Obstructive jaundice is characterized by increased concentration of conjugated bilirubin in serum, elevated levels of serum alkaline phosphatase, dark coloured urine and clay coloured feces sometimes with fat (Satyanarayana and Chakrapani 2022) [1].

Circumstances that may lead to jaundice

Despite the above stated causes of jaundice, there are some other conditions that may cause jaundice which include-

Physiological jaundice

Physiological jaundice is a mild form of jaundice that appears in > 50% of newborns as a result of immaturity of the liver enzyme in infants which is required to bilirubin conjugation. This mainly occurs in 2-4 days old infant and disappears by 7-10 days. If the jaundice appears early and persists for longer period, then the infant need immediate treatment (Suresh and Clark 2004) [13].

Gilbert's syndrome

Gilbert syndrome is an autosomal recessive disorder of bilirubin metabolism within the liver. In this condition, there is reduced bilirubin conjugation in the liver as a result of an inherited decrease in enzyme activity, thereby decreasing its excretion in the bile. As a result, the reduced bilirubin glucuronidation leads to hyperbilirubinemia (unconjugated) and repeated episodes of jaundice (Paul *et al.* 2004; Viveksandeep *et al.* 2022) [14, 15].

Dubin-Johnson syndrome

Dubin–Johnson syndrome is a rare, autosomal recessive, benign disorder that roots an isolated increase of conjugated bilirubin in the serum (GARD- an NCATS Program 2019) [16] which results in blackening of liver due to the deposition of a pigment similar to melanin (Strassburg 2010) [17]. This is an inherited disorder that weakens bilirubin secretion from liver cells after it has been conjugated resulting in intermittent jaundice (Wang and Wei-Feng 2014) [18]. It is usually asymptomatic, but may be diagnosed in early infancy based on laboratory tests. Generally no treatment is needed (Strassburg 2010) [17].

Rotor's syndrome

Rotor's syndrome is an inherited cause of mild intermittent jaundice and is similar to Dubin-Johnson syndrome without the retention of bilirubin in the liver cells (Huang *et al.* 2004) [19].

Crigler-Najjar syndrome

Crigler–Najjar syndrome is a rare inherited disorder that affects the bilirubin metabolism. The disorder results in a form of non-hemolytic jaundice, which results in high levels of unconjugated bilirubin and often leads to brain damage in infants. A gene nutation leads to a lack of the enzyme important for bilirubin conjugation that may lead to elevated bilirubin level (Cashore 2000; Orphanet 2021) [20, 21].

Haemolytic anaemia

Haemolytic anaemia is a form of anemia due to hemolysis, either in the blood vessels (intravascular hemolysis) or elsewhere in the body (extravascular). It most commonly occurs within the spleen, but can also occur in the reticuloendothelial system or mechanically in prosthetic valve damage. Haemolytic anaemia may be due to an abnormal haemoglobin variant in the RBCs, malaria, an autoimmune process or any other conditions that result to a significant elevation in the destruction of red blood cells and to an increase in the generation of bilirubin. The jaundice is mild and due to unconjugated bilirubin (Roche and Kobos 2004; Haley 2017) [4, 22].

Pseudojaundice:

Pseudojaundice is a jaundice in which the yellowness of the skin is due to consumption of large quantities of carrots, pumpkin or melon which contain beta-carotene. Pseudojaundice is a temporary and benign condition that is not related to bilirubin or bile (Watchko and Lin 2010) [23].

Diagnosis

Clinical History

Detailed medical history is needed. Proper data on various signs and symptoms (fever, loss of appetite, malaise, and muscle aches, nausea and vomiting, etc.) should be recorded which helps in establishing the differential diagnosis of jaundice.

Recording data on previous episodes of jaundice, the potential use of alcohol or drugs as well as previous surgeries or other illnesses. Family history is needed in order to evaluate possible inborn and familial conditions.

Physical Examination

Physical examination reveals yellow coloration of the skin and sclera and other tissues and is very important to determine the size of the liver while considering height and weight of the patient.

Laboratory Analysis

The aim of laboratory testing is to determine the cause of the jaundice and to evaluate the severity of the underlying condition. It mainly focused on the liver but specific additional tests, such as viral hepatitis testing or testing to evaluate increased RBC destruction, may be requested along with or following tests (Buiter *et al.* 2008) [24].

The Laboratory Tests include total bilirubin, Conjugated and unconjugated bilirubin, ALT (alanine aminotransferase), ALP (alkaline phosphatase), AST (aspartate aminotransferase), GGT (gamma-glutamyl transferase), total protein and albumin, haptoglobin and lactate dehydrogenase (LDH), Hepatitis A, B and C, Cytomegalovirus (CMV) accompanied with complete blood count, Reticulocyte count and prothrombin time (Taylor *et al.* 2012) [25].

Imaging Methods

Different imaging methods are available which are found to be helpful in differentiating the underlying etiology of jaundice adequately like abdominal ultrasonography (bile duct obstruction), color doppler ultrasonography and contrast-enhanced sonography (portal hypertension and small neoplasms), contrast CT (hepato-biliary pancreatic disease). Magnetic resonance is found useful in detection of focal liver lesions (Buckholz and Brown 2020) [26] and magnetic resonance cholangio- pancreatography (MRCP) plays an important role in detection of bile duct changes (Gurusamy *et al.* 2015) [27]. Endoscopy is essential to assess the presence of complications in esophageal and gastric varices when jaundice is due to liver cirrhosis (Mauro and Gadano 2020) [28].

Liver Biopsy and Transient Elastography

Liver biopsy is the preferred method for detection of the extend of liver damage (hepatocellular inflammation) but it is costly and invasive method which is mostly ultrasound (US) guided (Pimpin *et al.* 2018) [29]. Nowadays, liver biopsy has been replaced with a non-invasive cost-effective method, transient elastography which is helpful for the assessment of liver fibrosis (Milovanovic *et al.* 2017) [30].

Treatment

Treatment is fully dependable on the underlying cause of jaundice. Like in alcoholic hepatitis, treatment resume initiate with the cessation of alcohol consumption, in drug-induced hepatitis, treatment starts with the withdrawal of the suspected drug and in viral hepatitis antivirals are the method of choice etc. In patients with complete liver damage, liver transplantation is the only method of choice and in patients with obstructive jaundice, endoscopy as well as surgery remain the backbone of the therapy etc. Certain syndromes that cause jaundice like Gilbert syndrome, Rotor syndrome, and Dubin Johnson syndrome does not necessitates the need for treatment and also the treatment of pseudojaundice in cases of skin-coloring agents can be avoided.

Conclusion

Jaundice is rather considered as a symptom than as a disease. Jaundice is the yellow discoloration of the skin or sclera and mucous membranes due to defect in production, metabolism and excretion of bilirubin resulting in elevated bilirubin level in blood. The causes of jaundice may be either congenital or acquired. Serum bilirubin level and ultrasonography are used for differential diagnosis. High water intake and low-fat diet are best proper managements of jaundice. High water consumption along with low fat diet are considered best for proper management of jaundice. The treatment of jaundice varies with the on underlying cause of jaundice.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Satyanarayana U, Chakrapani U. Biochemistry. 6th Edn, Elsevier; c2022. p. 214-218.
2. Schwarzenbach HR. Jaundice and pathological liver values. Praxis (Bern 1994). 2013;102(12):727-9.
3. Leung TS, Outlaw F, MacDonald LW, Meek J. Jaundice Eye Color Index (JECI): quantifying the yellowness of

the sclera in jaundiced neonates with digital photography. Biomedical Optic Express. 2019;10(3):1250-1256.
4. Roche SP, Kobos R. Jaundice in the adult patient. American Family Physician. 2004;69(2):299-304.
5. Vítek L, Ostrow JD. Bilirubin chemistry and metabolism; harmful and protective aspects. Current Pharmaceutical Design. 2009;15(25):2869-2883.
6. Al Nasser Y, Jamal Z, Albugeaey M. Stat Pearls [Internet]. Stat Pearls Publishing; Treasure Island (FL), Carotenemia. Jan 24, 2022.
7. Kaneko, JJ, Harvey JW, Bruss ML. Clinical Biochemistry of Domestic Animals, 6th (Edn.) Academic Press, San Diego, USA; c2008.
8. Is Jaundice a disease or a symptom? Chennai Liver Foundation. Webmaster. 28th January 2022.
9. Hsia D. Bilirubin metabolism. Pediatric Clinics of North America. 1965;12:713-722.
10. Joseph A, Samant H. Jaundice. Last Update: May 8, 2022.
11. Telega GW. Jaundice. Nelson Pediatric Symptom-Based Diagnosis. Elsevier. edn 1; c2018. p. 255–274.
12. Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, Watchko JF. Hyperbilirubinemia in the newborn infant > or =35 weeks' gestation: an update with clarifications. Pediatrics. 2009;124(4):1193-1198.
13. Suresh GK, Clark RE. Cost-effectiveness of strategies that are intended to prevent kernicterus in newborn infants. Pediatrics. 2004;114(4):917-924.
14. Paul IM, Phillips TA, Widome MD, Hollenbeak CS. Cost-effectiveness of postnatal home nursing visits for preven tion of hospital care for jaundice and dehydration. Pediatrics. 2004;114(4):1015-1022.
15. Viveksandeep TC, Thomas WF, Savio J. Gilbert Syndrome. National Library of Medicine. The National Center for Biotechnology Information, February 14, 2022.
16. Dubin-Johnson syndrome. Genetic and Rare Diseases Information Center (GARD) – an NCATS Program. rarediseases.info.nih.gov. Retrieved 11 April 2019.
17. Strassburg CP. Hyperbilirubinemia syndromes (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor syndrome). Best Practice and Research: Clinical Gastroenterology. 2010;24(5):555-571.
18. Wang L, Wei-Feng F. Obstructive jaundice and perioperative management. Acta Anaesthesiologica Taiwanica. 2014;52(1):22-29.
19. Huang MJ, Kua KE, Teng HC, Tang KS, Weng HW, Huang CS. Risk factors for severe hyperbilirubinemia in neonates. Pediatric Research, 2004;56(5):682-919.
20. Cashore WJ. Bilirubin and jaundice in the micropremie. Clinics in Perinatology. 2000;27:171-179.
21. Reserved, INSERM US14 All rights. Orphanet: Crigler Najjar syndrome. www.orpha.net. Retrieved 10th March 2021.
22. Haley K. Congenital hemolytic anemia. Medical Clinics of North America. 2017;101(2):361-374.
23. Watchko JF, Lin Z. Exploring the genetic architecture of neonatal hyperbilirubinemia. Semin Fetal Neonatal Med, 2010;15:169-175.
24. Buiter HD, Dijkstra SS, Oude Elferink RF, Bijster P, Woltil HA, Verkade HJ. Neonatal jaundice and stool production in breast- or formula-fed term infants. The European Journal of Pediatrics. 2008;167(5):501-507.
25. Taylor A, Stapley S, Hamilton, W. Jaundice in primary care: a cohort study of adults aged >45 years using electronic medical records. Family Practice. 2012;29(4):416-420.
26. Buckholz AP, Brown RS. Cholangiocarcinoma: diagnosis and management. Clinical Liver Disease. 2020;24(3):421–436.
27. Gurusamy KS, Giljaca V, Takwoingi Y, Higgie D, Poropat G, Štimac D *et al*. Endoscopic retrograde cholangiopancreatography versus intraoperative cholangiography for diagnosis of common bile duct stones. Cochrane Database Systemic Review. 2015;(2):CD010339.
28. Mauro E, Gadano A. What's new in portal hypertension? Liver International. 2020;40(1):122- 127.
29. Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, *et al***.** Burden of liver disease in Europe: epidemiology and analysis of risk factors to identify prevention policies. Journal of Hepatology. 2018;69(3):718-735.
30. Milovanovic AT, Stojkovic LM, Dumic I, Jocic N, Pavlovic MA, Dragasevic S, *et al*. Diagnostic accuracy of platelet count and platelet indices in non-invasive assessment of fibrosis in non-alcoholic fatty liver disease patients. Can J Gastroenterol Hepatol. 2017, 6070135.